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Case Report

A case of neonatal pulmonary *Aspergillosis* successfully treated with micafungin

Running title: A case of neonatal pulmonary *Aspergillosis*

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Abstract

Preterm infants are susceptible to opportunistic infection because of their immature immune system. As to fungal infection, *Aspergillosis* is second only to *Candida* infection in these patients.

Here we report the case of an extremely low birth weight (ELBW) infant who developed pulmonary *Aspergillosis* and was successfully treated by micafungin (echinocandins). The infection occurred in the cavity in chronic lung disease and was diagnosed by typical CT imaging and detection of *Aspergillus* galactmannan antigen in the serum specimen. To our knowledge, this is the first report of pulmonary *Aspergillosis* treated with micafungin in ELBW infants.

Keywords: preterm infant, pulmonary *Aspergillosis*, micafungin

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Introduction

Improvement of perinatal and neonatal care has resulted in the increased survival of extremely low birth weight (ELBW) infants, but invasive fungal infection is one of the leading causes of morbidity. In addition to their immature immune system, the presence of a central catheter, endotracheal tubes, and many drugs, including broad-spectrum antibiotics and glucocorticoids, aggravates their susceptibility to fungal infections. Invasive *Candidiasis* is a leading cause of infection-related mortality in ELBW infants, and neonatal cases of pulmonary candidiasis have already been reported or reviewed[1]. By comparison, there are very few reports about *Aspergillosis* except for sporadic cases of invasive pulmonary *Aspergillosis* (IPA), especially *Aspergilloma*. As the invasive *Aspergillosis* is a major threat for preterm infants due to high morbidity and mortality rates [2,3,4], the most important issue is an early diagnosis before dissemination and an appropriate choice of antifungal agents.

Here, we report the case of a neonate with pulmonary *Aspergillosis*. The diagnosis was made by typical CT imaging and abnormal elevation of serum galactomannan antigen. Although he had many risk factors, he was successfully treated with micafungin without complications.

Case Report

A male pre-term infant was admitted to our NICU after delivery at 25 weeks and 3 days of gestation (birth weight 808g) by emergent cesarean section because of uncontrollable uterine contractions associated with chorioamnionitis. Apgar scores were 1 and 4 at 1 and 5 minutes, respectively. He was immediately intubated and artificial ventilation was started. Although he had no sign of RDS, he had significant persistent ductus arteriosus and was treated with indomethacin and surgical ligation. From 3 days of age, his serial chest radiographs gradually showed a reticulogranular pattern (Figure 1), so we started inhaled steroid therapy using 50 μ g fluticasone propionate twice daily from 4 days of age. Then, at 17 days of life, the infant developed oligourea and hypotension with hyponatremia, and late-onset circulatory dysfunction was suspected. We stopped inhaled steroid therapy and started systemic steroid administration. Total doses of systemic steroid, from 17 to 63 days of age, were 48.5mg of hydrocortisone and 3.55mg of dexamethasone. During steroid therapy, he suffered from methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia from 27 days of age and CRP elevated to 8.0mg/dl. He recovered after treatment with antibiotics (teicoplanin) and gammaglobulin but multiple bulla formation in the bilateral lung field emerged.

He was extubated from mechanical ventilation at 38 days of life and was then put on nasal CPAP (continuous positive airway pressure). He discontinued nasal CPAP at 64 days of age,

but required low-flow oxygen via a nasal cannula. He was reintubated twice for a short period, at 60 and 76 days of life, because he needed laser photocoagulation therapy for retinopathy of prematurity.

From about 60 days of life, his laboratory investigation showed low positive C-reactive protein and leukocytosis, and chest radiograph revealed a solid round infiltration in the middle lobe of the right lung. We started antibiotic therapy with teicoplanin and ceftazidime from 76 days of age, but CRP did not normalize. Laboratory findings at 82 days of age showed weakly positive β -D-glucan at 6.608 pg/ml (the kinetic turbidimetric Limulus method [Beta-Glucan test; Wako]; normal range <3.95pg/ml) with WBC 14,200/ μ l and CRP 0.7mg/dl. High-resolution CT of the lung revealed a ball-like cavity in the right middle lobe with fluid collection, called “air space consolidation” (Figure 2), which was identified by transthorathic echography (transducer is placed in the fourth or fifth left intercostal space on the midaxillary line).

We used fluconazole as the first-line drug for 2 days, and then replaced it with micafungin because ELISA for galactomannan aspergillus antigen proved to be positive (the index was 2.3; normal range is <0.5). Initially we started at a dose of 2 mg/kg/day over 1 hour for 2 days, and then, increased up to 5mg/kg/day and maintained for 21 days from 89 to 109 days of age. After the initiation of micafungin, he showed neither symptoms related to fungal infection nor adverse events associated with the treatment. The lesion had almost

disappeared on chest CT imaging at 131 days of age and serum galactomannan antigen became negative at 141 days of age, lower than 0.5 (the index was 0.3).

He was discharged from our NICU at 150 days of age without any complications. Now he is 3 years old and has not experienced any signs of recurrence of *Aspergillus* infection.

We measured the serum concentration of micafungin twice. The first time, from 97 to 98 days of age, peak and trough concentrations were 8.6 and 6.39 μ g/ml, respectively. From 108 to 109 days of age, these were 3.98 and 1.29 μ g/ml, respectively. Although the concentrations of the medicine were lower than expected, his clinical course was acceptable and we did not increase the dosage.

We found no immune dysfunction, including the superoxide production ability and phagocytic function of neutrophils.

Discussion

Nosocomial *Aspergillus* infection represents a serious threat for severely immunocompromised patients [5]. Prematurity is a risk factor for invasive *Aspergillosis*, and a birth weight of <1500g is also considered as a risk factor [6]. Preterm neonates have several risk factors, including cavitory lung disease, steroid use or immaturity of the immune system[7]. In adult patients, the infection mostly strikes the lung. Invasion by the fungus usually follows its inhalation and colonization of airways, and cutaneous *Aspergillosis* is reported as a late manifestation of haematogenous dissemination. In contrast to the adults, because of the immature skin, superficial skin infections are considered important as the first colonization of *Aspergillus* in preterm neonates [8].

Our patient had all of these risk factors, developed pulmonary *Aspergillosis* and is considered a typical case; however, no cutaneous lesion was found and skin colonization was not detected throughout his clinical courses. We suspect that inhaled pores accumulated in small cavities associated with BPD, where macrophages could not reached. Our case suggested that cutaneous lesions did not always precede invasive *Aspergillus* infection and that negative skin surveillance results did not reduce its possibility.

Diagnosis is divided into three categories; proven, probable, and suspected invasive fungal infection[9]. Proven infection requires detection of the fungus itself, but definitive diagnosis by tissue microscopy and culture is difficult in the early stage of infection, and is

too invasive for neonates. *Aspergilloma* was therefore diagnosed from his clinical course, typical pulmonary CT imaging and serum galactomannan antigen. Even mild increase of galactomannan antigen could be diagnostic for *Aspergillosis* [10,11], and the importance of a regular survey of galactomannan antigen was reported by Sulahian [12]. In our case, CRP and β -D-glucan was slightly increased, and the X-ray showed a cavity in the lung regardless an antibiotic therapy, so we suspected *Aspergillus* pneumonia and diagnosed “probable *Aspergilloma*” due to positive galactomannan antigen (2.3).

Antifungal therapy has changed by the innovation of new anti-fungal agents during the past decade. New agents are expected to have a broader spectrum with fewer side effects, and their efficacy and safety have been intensely investigated in adults but an information for children is still limited [8,13,14,15]. Antifungal agents commonly used are classified into four categories: polyene macrolides, fluorinated pyrimidines, triazoles, and echinocandins[16]. Prasad et al. surveyed the trend for anti-fungal therapy in pediatric patients from 2000 to 2006 [17]. Based on their report, the most commonly prescribed antifungal agent was fluconazole (76%), followed by amphotericin preparations (26%). Prescriptions for voriconazole and echinocandin are steadily increasing and replacing amphotericin B (AMB) for the treatment of *Aspergillosis* [18,19]. But the increase in echinocandin use was almost entirely attributable to the use of caspofungin [20], and reports of infants treated with micafungin are exclusively limited. Micafungin is a new echinocandin that works by inhibiting

1,3- β -D-glucan synthesis, an enzyme responsible for fungal cell wall synthesis, and it is licensed in Japan as the only medicine for pediatric invasive fungal infections. Micafungin has a broad spectrum for candida and *Aspergillus* species. There are reports on the pharmacokinetics data for micafungin in preterm infants[21,22,23,24,25], which exhibited a linear plasma pattern in the range 0.25-16mg/kg[26]. In our case, administration of 5mg/kg/day micafungin for three weeks resulted in a relatively low plasma concentration compared to the report for adults, however, the anti-fungal effects were sufficient, and no side effects were observed.

Our limited experience suggested that micafungin could be a good choice for the treatment of infants with invasive *Aspergillosis*.

Conclusion

We experienced an extremely preterm male infant infected with probable pulmonary *Aspergillosis*. The detection of *Aspergillus* was difficult but serum galactomannan antigen was useful for the diagnosis. Administration of 5mg/kg/day micafungin for three weeks resulted in clinical improvement without complications, and we consider that micafungin could be a good choice not only for adults but also infants.

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Disclosure Statements

We do not have any potential or actual interests which are disclosed.

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Figure legends

Fig. 1. Chest radiography of the infant showing reticulogranular pattern of the whole lobes.

Fig. 2. Computed tomography of the right middle lobe showing a ball-like cavity with fluid collection

Fig. 1.

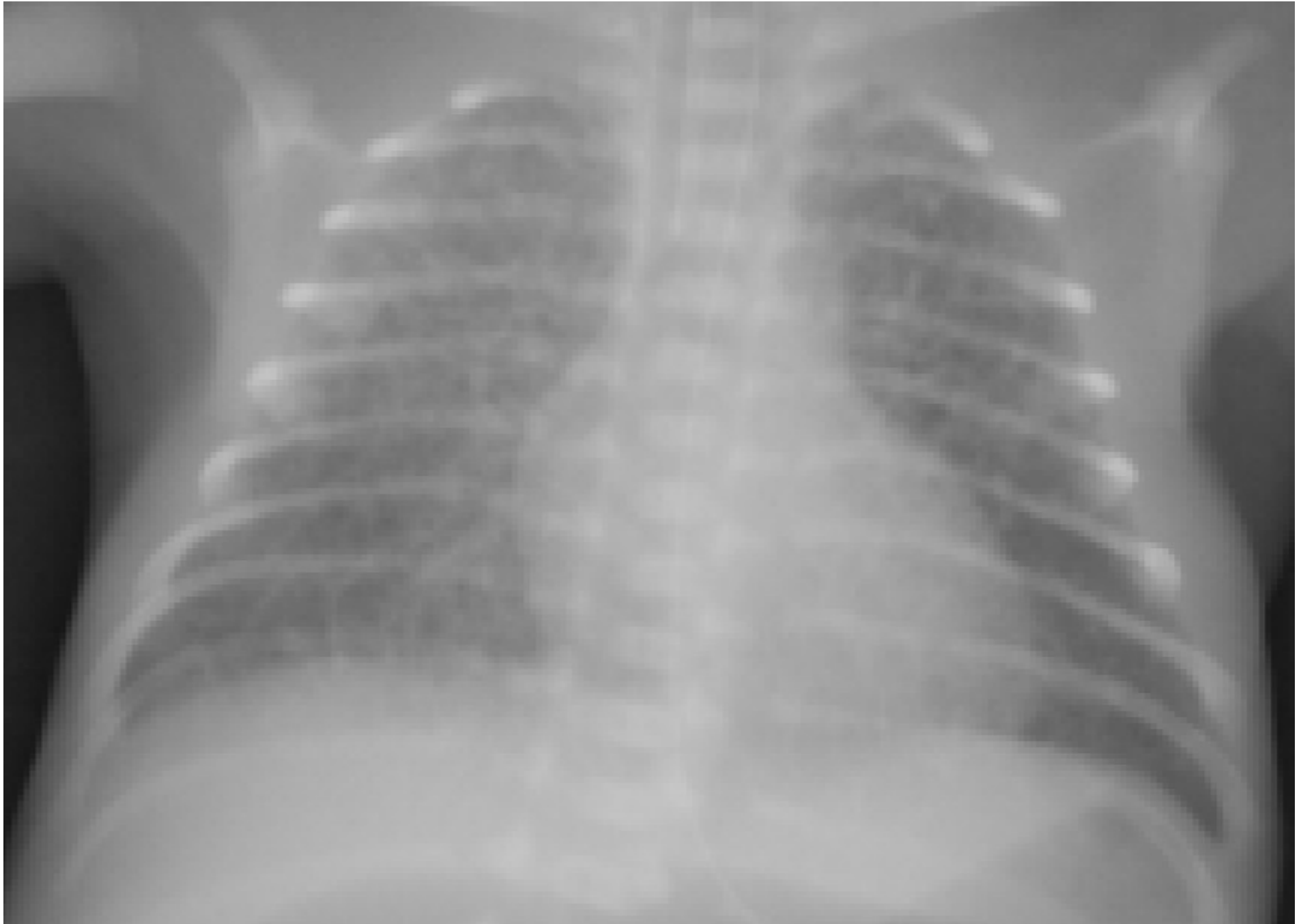


Fig. 2.

